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SERUM THYROID HORMONE LEVELS AND OUTER-RING MONODEIODINATION OF THYROXINE IN RABBITS TREATED WITH DIFFERENT AMOUNTS OF PERCHLORIC ACID AMMONIA (PAA)

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Introduction

Antithyroid drugs are widely used in order to improve average daily gain (McDonald, 1977). One of these drugs is perchloric acid ammonia (PAA) , the action mechanism of that was studied as early as 1964 by Wolff. The benevolent effect of it on the weight gain was studied by the authors (Gippert et al., 1984) concerning rabbit nutrition. The effect of this drug upon thyroid economy in rabbits was investigated in this paper in order to get further information about how PAA influences thyroxine secretion and metabolism. Since it has been proved (Silva and Larsen, 1983) that thyroxine can be monodeiodinated in the liver (and other tissues) and activation (T3 formation) or inactivation (reverse-T3 formation) processes can be involved in the peripheral thyroid hormone metabolism (Larsen et al., 1984), it seemed intriguing to investigate monodeiodination in response to an antithyroid drug. Also it was the aim of the present study to establish a model system for investigating antithyroid compoud effect of feeds upon peripheral thyroid hormone metabolism.

Materials and Methods

40 New Zealand White rabbits were kept in the animal room of the Isotope Lab (Univ. Vet. Sci.). Animals were fed ad libitum and water was available continuously via automatic watering troughs. After a week of adaptation period the animals were allotted into four groups: controls or no treatment (group I.); 15 mg (group II.), 30 mg (group III.) and 60 mg (group IV.) PAA/kg body weight p.o. daily during 15 days. Animals were 6 weeks old at the beginning of the experiment. Blood samples were taken from 20 animals on day 0 (this served as basic control serum for thyroid hormones), then on days 5, 10 and 15 after beginning of the PAA treatments. On day 15 animals were exsanguinated from the carotis arteria, liver, thyroid gland and adrenal gland were taken out, weighted freshly and deep frozen (-20°C) until further analysis. Body weight was checked every 4th day throughout.

Serum samples were analysed for triiodothyronine (T3) and thyroxine (T4) content according to the RIA procedure described earlier (Pethes et al., 1978). Intraassay and interassay errors were lower than 5 and 9 percent, respectively.

The liver 5'-deiodinase activity was measured according to that published lately (Rudas, 1986). Briefly, homogenates were prepared from 1 g of liver tissues with phosphate buffer (0.15 M, pH 7.4). After centrifugation (700 g, 4°C, 20 min.) supernatans were incubated with or without 0.6 umol T4 (Sigma, St.Louis) for one or 4 hours in the presence or absence of propylthyouracyl. After the given period monodeiodination was stopped by giving ethanol (ice cold, 96 %) to the incubation mixture (being kept at 37°C until this step). T3 content of the differently treated homogenates was determined by RIA (see before). The activity of the 5'-deiodinase was expressed as pg T3 produced/mg protein incubate/hour. Comparison of results was made using Student's t-test as described by Snedecor and Cochran (1967).

Results

The body weigth of the animals in group II. was significantly ($p < 0.05$) higher than in the other three groups (mean ± SEM /n/ g: I.: 1101 ± 107 /10/; II.: 1261 ± ± 82 /10/; III.: 1093 ± 84 /10/ and IV.: 1024 ± 56 /10/. Liver weights, expressed in percentage of body weight were not different in the four groups (data not given). Table 1 demonstates the weights of thyroid and adrenal glands after 15 days of treatment with PAA. While adrenal weights were not differing from the control values, the weight of thyroid changed significantly ($p < 0.05$) as an effect of PAA treatment. It is lower in group II. and higher in group III. and IV. than that of the control (I).

The serum levels of thyroid hormones have changed significantly owing to the treatment (see Figure). There were no changes in the thyroxine or triiodothyronine serum level of the control group (I.). Low dose (II.) of PAA caused transient elevation of both thyroid hormone levels, while higher doses (III. and IV.) depressed serum thyroid hormone concentrations throughout the experiment. It should be noted however that even 60 mg PAA per kg body weight per day cannot depress serum T4 or T3 levels into the hypothyroid range.

One can observe that tissue thyroid hormone concentration as judged from the T3 content of the liver (Table 2) is higher in PAA treated groups ($p < 0.05$).

Monodeiodase activity in the liver of rabbits treated with 15 mg PAA (II.) is not different from that found in control animals (group I.), at day 15 of the treatment (Table 3). In those rabbits who received higher doses of PAA (III., IV. there exists a higher level of 5'-deiodinase activity ($p < 0.05$).

Discussion

As it was stated earlier by the authors (Gippert et al., 1985), PAA enhanced also in this experiment the ADG if administered at a dose of 15 mg/kg BW/day. This amount of the drug seems to cause only a transient effect on the thyroid hormone level of the serum (Figure) and does not influence the 5'-deiodinase activity (Table 3). However, tissue T3 content (Table 2) and thyroid weights (table 1) are indicating that both central and peripheral parts of thyroid economy are affected by the administration of the compound. Present data suggest in this way that after 5 days the drug evokes a stimulatory effect on the secretion of the thyroxine, supposedly after having been depressed thyroxine secretion and thus provoking higher TSH production. Later on the depressing effect on T4 secretion outweights the stimulatory effect of TSH and therefor serum level will drop. The higher tissue T3

content is indicative of the lower T3 metabolis, which prevents T3 to drop to the hypothyroid level (i.e. below than 0.2 ng/ml : McBridge and Cramner, 1978).

In the two other groups one can see a continuous drop of serum T4 and T3 (Figure, panel III., IV.) and a concommittant higher tissue T3 level together with increased 5'-deiodinase activities. These phenomena indicate that while the compound is able to suppres T4 secretion from the thyroid gland and the high dose prevents the thyroid to be able to respond on the TSH (cf. I., II. vs. III., IV. on the 5th day of treatment) the peripheral deiodination of thyroxine enhances and produces more active T3 available for the peripheral cells.

In other species it has been demonstrated (Silva and Matthew, 1984; Rudas and Pethes, 1986) that peripheral thyroid hormone deiodination can serve as a regulating mechanism producing more or less active T3 from the T4 secreted from the thyroid gland. Since it has been shown (Slebodzinsky and Gawecka, 1983; Ogaidsanov et al., 1970) that outer ring monodeiodination is involved also in the thyroid economy of the rabbit, one may suppose that normal tissue levels of thyroid hormones can be maintained by two mechanisms in this species too. The major factor should be the normal secretion of thyroxine from the thyroid gland and the other one is the metabolic rate of this hormone on the periphery. The latter one can be influenced by several factors: 1. protein binding of thyroxine in the blood, 2. rate of metabolic routes other than deiodination, 3. metabolic rate of the products of deiodination and 4. tissue level and activity of the deiodinase enzyme complex (for review see Silva and Larsen, 1983; Larsen et al., 1984). Thus results obtained here should be interpreted carefully.

In conclusion one can state that the PAA, acting upon the thyroid itself, influences directly the peripheral metabolism of thyroid hormones in rabbits. The benevolent effect of this compound on average daily gain, as shown by the authors earlier and in this experiment, can hardly be explained by the effect of the low dosis of PAA on thyroid economy. A much plausible reason for the action mechanism can be indirect : 1. changing motility of the intestine and thus promoting absorption (Ogaidsanov et al., 1970), 2. changing the absorption characteristics of nutrients probably via increased thyroid hormone level. A tentative effect of PAA on the composition of intestinal flora can be ruled out according to recent results (Szita and Fekete, 1985).

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Figure legend

The level of thyroid hormones (thyroxine, T4; triiodothyronine, T3) in the serum of rabbits treated with different amounts of perchloric acid ammonia (PAA). Panel I.: control, non-treated; panel II.: 15 mg/kg BW po., daily, from day 0 up to day 15, ; panel III.: 30 mg/kg BW; panel IV.: 60 mg/kg BW.

Table 1. : The weight of thyroids and adrenal glands of rabbits treated with different levels of PAA

		I. control	II. 15 mg PAA	III. 30 mg PAA	IV. 60 mg PAA /kg BW
TH.	x	135	68*	199*	182*
	SEM	20	8	17	20
	n	9	10	10	10
ADR.	x	76	68	74	73
	SEM	8	7	6	3
	n	10	10	10	10

TH. = thyroid, mg ; ADR. = adrenal, mg

*) $p < 0.05$ vs control

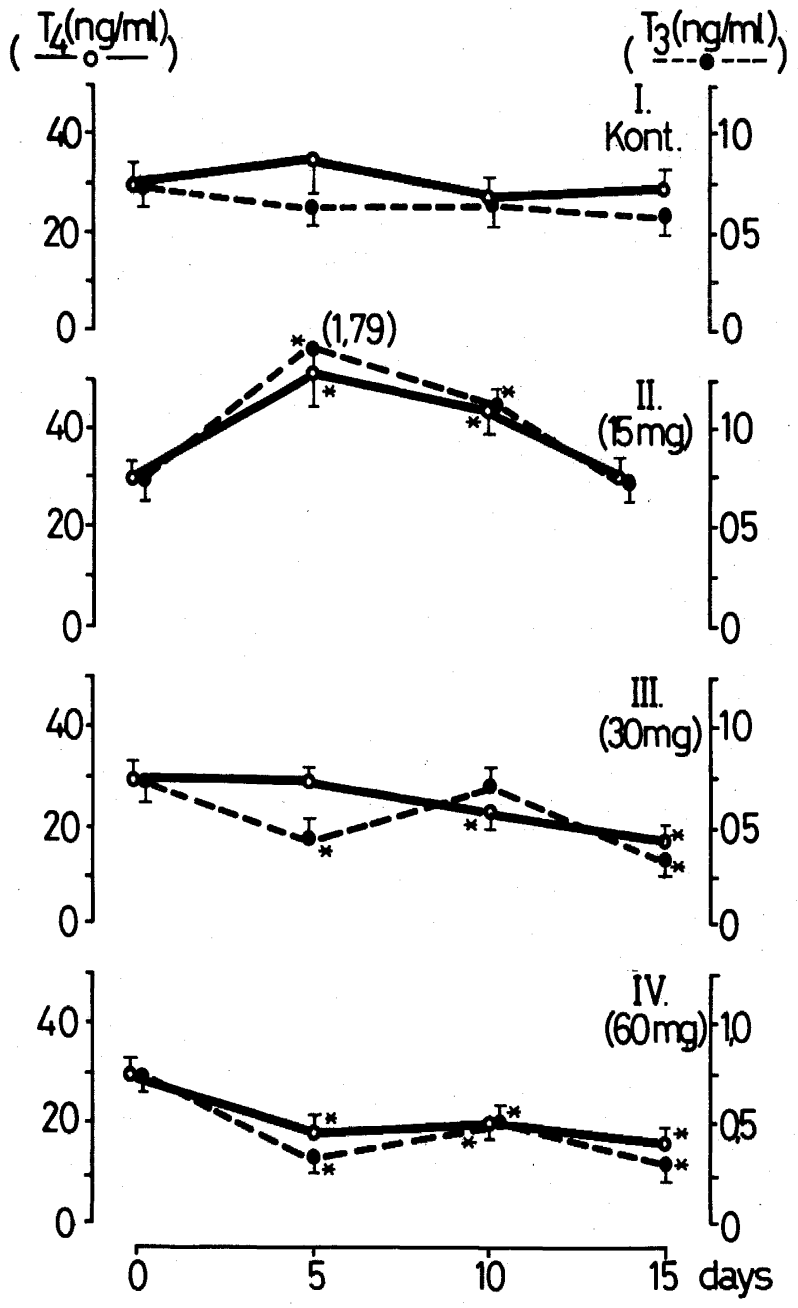
Table 2 : Tissue level of triiodothyronine in the liver of rabbits treated with different amounts of PAA (perchloric acid ammonia)

		I. control	II. 15 mg PAA	III. 30 mg PAA	IV. 60 mg PAA
T3 (ng/100 mg protein)	x	82	97*	96*-	109*
	SEM	4	3	6	10
	n	10	10	10	9

Table 3: Liver 5'-deiodase activity in rabbits treated with different amount of PAA

		I. control	II. 15 mg PAA	III. 30 mg PAA	IV. 60 mg PAA
T3 (pg) hr/mg protein	x	413	479	592*-	513*-
	SEM	23	33	47	15
	n	10	10	6	10

*-) $p < 0.05$ vs control


T4(ng/ml)
T3(ng/ml)
I.
Kont.
(1,79)
II.
(15mg)
III.
(30mg)
IV.
(60mg)
40
20
0
10
05
1,0
0,5
0
5
10
15
days

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The present experiment was undertaken to investigate the effect of an antithyroid, perchloric acid ammonia (PAA) on rabbits treated with 0 (I.), 15 (II.), 30 (III.) and 60 mg/kg BW PAA (IV.) daily for 15 days. T4 and T3 blood serum levels dropped significantly ($p<0.05$) in groups III. and IV. Tissue triiodothyronine content was higher ($p<0.05$) in all groups (II., III., IV.) treated with PAA while the activity of the 5'-monodeiodinase in the liver was higher only in the two groups (III. and IV.) receiving high doses.

LA TENEUR DU SERUM EN HORMONES THYROIDIENNES ET MONODEIODINATION DE THYROXINE CHEZ LES LAPINS TRAITÉS DE L'AMMONIUM - PERCHLORATE

Cet essai a été exécuté pour étudier l'effet d'un antithyroidien, l'ammonium-perchlorate (AP) sur les lapins, traités par 0 (I.), 15 (II.), 30 (III.) et 60 (IV.) mg/kg PV AP par jour, pendant deux semaines. T4 et T3 concentration du sang a été baissée significativement ($p<0.05$) dans les groupes III. et IV. La teneur en T3 des tissus a été plus élevée ($p<0.05$) chez tous les groupes, traités de l' AP. L'activité de 5'-monodeiodinase dans le foie a été plus haut seulement chez les animaux, reçus les doses 30 et 60 mg/kg PV.